REMARKS

Claims 1-66 are pending. Claims 11-23, 44-48 and 61 have been withdrawn from consideration. Claims 1-10, 24-43, 49-60 and 62 to 66 stand variously rejected under 35 U.S.C. § 112, first and second paragraphs. In view of the following remarks and foregoing amendments, Applicants respectfully request reconsideration of the application.

Overview of the Amendments

Claims 1 and 2 have been amended to specify that sequence "having at least 90% identity to..." is a nucleotide sequence. Support can be found throughout the application and claims as originally filed. Claim 9 has been amended to specify that the sequence encoding the HIV polymerase includes deletions in the coding region encoding reverse transcriptase or integrase, as described, for example, on page 68 of the specification. Claim 10 has been amended to specify that the polypeptide comprises certain epitopes as described, for example, on page 69 of the specification. Claims 24, 27, 41, 42 and 69 have been amended to correct antecedent basis. Finally, claim 63 has been amended to clarify that the polypeptide is derived from HIV, as described for example, on page 11 of the specification.

New claims 67-77 have been added. These new claims find support throughout the specification and claims as originally filed. Furthermore, Applicants note that the Office has indicated that the new claims are fully enabled by the specification as filed.

The amendments are made to expedite prosecution and are not made for reasons related to patentability. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

Information Disclosure Statement

The Examiner has objected to the IDS filed October 24, 2000 because it did not properly cite the journal article(s) listed on the 1449. Submitted herewith is a new 1449 including the titles of the journal articles. Applicants respectfully request that the Examiner initial the new 1449 forms.

Restriction Requirement

Applicants acknowledge with appreciation the withdrawal of the restriction as between groups I-XVI as well as withdrawal of the election of species requirement. Thus, claims 1-10, 24-43, 49-60 and 62-66 (Group I) are pending and have been examined. Applicants expressly reserve their right under 35 USC §121 to file one or more divisional applications directed to the nonelected subject matter during the pendency of this application.

35 U.S.C. 112, First Paragraph

Claims 1-10, 24-43, 49-60 and 62-66 stand rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. In particular, it is alleged that while the specification is enabling for (1) an expression cassette comprising a polynucleotide sequence encoding a Gag polypeptide as set forth in SEQ ID NO:1 or 2; (2) an expression cassette comprising a polynucleotide sequence as set forth in SEQ ID NO:3 or 4; (3) the expression cassette of (1) further comprising a sequence encoding an HIV protease polypeptide; (4) the expression cassette of (2) further comprising a sequence encoding an HIV protease polypeptide; (5) the expression cassette of claim (2) further comprising a sequence encoding an HIV polymerase polypeptide; (6) a composition for generating an immune response in a mammal comprising the expression cassette of (1); (7) a method for generating an immune response in a mammal comprising intramuscularly administering the expression cassette of (1) to a mammal, it is does not enable the rest of the claims. (Office Action, page 5). The Examiner also cites several references in support of the enablement rejection, alleging that the state of the art in vaccines is unpredictable. (Office Action, pages 6-7). Additionally, it is alleged that it would require undue experimentation to make and/or use sequences having at least 90% identity to those presented as SEQ ID NOs:1-4. (Office Action, page 8).

Applicants traverse the rejections and supporting remarks.

Before addressing each issue raised by the Office, Applicants note the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without

undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the Applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). For the reasons detailed below, the Office has failed to establish a *prima facie* case of non-enablement.

Immunogenic Compositions and Methods of Inducing an Immune Response

Applicants also note that is well-settled that the enablement requirement is satisfied if the applicant's specification teaches one of skill in the art how to make and use the claimed invention without undue experimentation. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Further the "invention" referred to in the enablement requirement of section 112 is the claimed invention." *See, Christianson v. Colt Industries Operating Corp.* 3 USPQ2d 1241 (Fed. Cir. 1987), emphasis added. Thus, the Office must first determine what each claim recites when the claim is considered as a whole, not when its parts are analyzed individually. See, Training Manual on Enablement, page 9. Moreover, the existence of inoperative or ineffective embodiments does not mean that the enablement requirement if not satisfied. Indeed, if any use of multiple uses disclosed in the specification are enabled, the application is enabling. See, Training Manual, page 21.

In the pending case, the Office acknowledges that the claims are enabled for specific sequences and use of these sequences to generate immunological responses in mammals when administered intramuscularly. (Office Action, page 5). However, in support of the enablement rejection, the Examiner cites numerous references allegedly showing the unpredictability of nucleic vaccines, particular in the filed of HIV (citing Gurunathan, Anderson and Verma).

As a threshold matter, Applicants note that the pending claims 1-10 are directed to expression cassettes and pending claims 24-41 are directed to recombinant expression systems and cells comprising these expression cassettes and expression

systems. Only examined claims 42, 43, 49-60 and 62-66 are directed to methods of generating an immune response and none of these claims recite "vaccine compositions" or "methods of treating (or vaccinating against) HIV." Rather, they are drawn to compositions comprising particular sequences or to methods of generating an immunological response in a mammal using these compositions. As is well-known and described, for example, on page 14, lines 3-12 of the specification, an immunological response can be either a humoral immune response (*e.g.*, mediated by antibodies) or a cellular immune response (*e.g.*, mediated by T-lymphocytes and/or other white blood cells). Therefore, when properly interpreted in light of the specification, the pending claims are directed to methods of eliciting cellular and humoral immune responses and the enablement requirement is satisfied by Applicants' showing that these methods elicit both humoral and cellular immune responses. (See, Examples and attached Exhibit A showing that the claimed expression constructs generate a cellular immune response when administered to mice).

Furthermore, Applicants submit that the Office cannot reject the claims on the basis that one "implied" use may be ineffective or inoperative. In other words, the fact that the enabled cellular and humoral immune responses may or may not be protective and/or therapeutic against HIV is not relevant to the enablement inquiry in this case. As noted above, all that is required to satisfy enablement is that specification enable one use. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976). In the case at hand, there is no dispute that Applicants have enabled methods of eliciting an immunological response in a subject using an expression cassette as claimed. (See, attached Exhibit A) Thus, Applicants have plainly shown how to make and use the claimed invention and Applicants are not required to establish whether these immunological responses are protective or therapeutic. In sum, Applicants' specification fully enables the pending claims by enabling not only a single use, but by enabling the claims throughout their scope.

Applicants also traverse the Examiner's assertion that the gene therapy references establish that the claimed invention is unpredictable. (Gurunathan, Verma and Anderson, cited on pages 6-7 of the Office Action). These references do no such

thing. None of these reference address using the particularly claimed expression cassettes to generate an immune response. Gurunathan is directed to the use of CD40LT as an adjuvant. Anderson is directed a gene-therapy in the context of treatment regimes. Similarly, Verma is directed to issues involved in "alleviating the symptoms of disease" (See, Abstract). Thus, these references are a far cry away from establishing that methods of eliciting immune responses to the claimed expression cassettes are not enabled by Applicants' specification. In fact, Applicants' specification describes and demonstrates the generation of an immune response and, accordingly, the various references cited by the Office are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed invention.

Despite the failure of the Office to make a case for non-enablement, Applicants address why the claims are enabled throughout their scope. As previously discussed, enablement is fact-dependent. An applicant does not need to specify the dosage or method of use if it is known to one of skill in the art that such information could be readily obtained. *See, e.g.*, USPTO Training Materials on Enablement, page 20. In fact, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which experimentation should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention. *Ex parte Forman, supra*; *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Further, the standards articulated in *In re Wands* can be used to help determine whether the specification at issue is in fact enabling. Indeed, the situation in *Wands* is highly analogous to that at hand. In *Wands*, the Federal Circuit held that claims to generic monoclonal antibodies were enabled by a specification that taught the entire procedure of making monoclonal antibodies. Moreover, in view of the high level of skill in the art and routine nature of each step of the antibody-making procedure, the court held that the amount of experimentation required to make other monoclonals was extensive, but not undue.

Similarly, in the pending case, Applicants submit that their specification clearly sets forth the procedure for determining routes of administration of expression cassettes as well as dosages and delivery regimes. Applicants direct the Examiner's

attention to Examples 4-7 and the attached Exhibit A that demonstrates the claimed expression constructs induce an immune response in a mammal when made, administered and tested for immunogenicity following the teachings of the specification. (See, for example, Section 2.3 of the specification, pages 50 to 61 regarding administration; page 76 for assessing immunogenic responses). Thus, Applicants have rebutted any allegation that the specification does not fully enable the claims and that there is more than sufficient guidance as to the claimed methods in the specification.

Percent Identity

The Examiner also asserts that the specification does not provide sufficient description for one of skill in the art to make and/or use a sequence having "90% identity" to the sequences of SEQ ID NO:1 to 4. Applicants disagree with the Examiner's assessment of the level of enabling disclosure in the present applicant in regard to "percent identity." The use of available programs for calculating identity or similarity between sequences is fully disclosed in the specification, for example at page 17, line 3 to page 20. Exemplary default parameters for these available programs are set forth, on page 17, lines 28-29 and page 18, lines 3-9. These programs and parameters were also used and are exemplified at page 71. Indeed, the use of such default parameters is routine and well within the abilities of one having ordinary skill in the art -- this is the manner in which the Patent Office searches the database for sequences that may correspond to the claimed sequences.

In sum, when evidence of record is examined, Applicants submit that it is plain that it would not require undue experimentation to practice the claimed invention, given the guidance found in the specification and state of the art. The claimed invention is, therefore, fully enabled by the specification and Applicants respectfully request the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

35 U.S.C. 112, Second Paragraph

Claims 1, 2, 9, 10, 24, 27, 42, 49, 59, 62 and 63 stand rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite. Applicants address each rejection in turn below.

Claims 1 and 2 are alleged to be indefinite because it is not specified whether "a sequence" is referring to the Gag polypeptide sequence or another sequence. Applicants note that claims 1 and 2 are directed to polynucleotide sequences encoding a Gag polypeptide wherein said polynucleotide sequences have at least 90% sequence identity to ..." Thus, the claims are clear that the recitation of a "a sequence" refers to the Gag-encoding polynucleotide sequence, not to the amino acid sequence of the Gag polypeptide. Nonetheless, solely to advance prosecution and without conceding the correctness of the Examiner's position, claims 1 and 2 have been amended herein to specify the sequence is a nucleotide sequence.

Claim 9 is alleged to be indefinite due to the use of the term "corresponding." Although Applicants traverse the rejection, claim 9 has been amended herein to remove the term "corresponding." The amendment is made solely to advance prosecution and without conceding the correctness of the Examiner's position.

Claim 10 is alleged to be indefinite due to the use of the term "preserve." Applicants submit that the term is clear to one of skill in the art in view of the specification. Nonetheless, in order to advance prosecution, the claim has been rewritten herein to obviate the rejection.

Claims 24, 27, 49, and 62 are alleged to be indefinite for failing to point to expression cassettes by the use of the term "the." Applicants have corrected these typographical errors herein, thereby obviating the rejections.

Claim 63 is alleged to be indefinite in the recitation of "HIV-derived." Because one of skill the art would understand the metes and bounds of this term, Applicants traverse. For example, on page 20, lines 11-13, Applicants set forth what it means for a polypeptide to be derived from another. Nonetheless, in order to advance prosecution, the claim has been rewritten herein to obviate the rejection.

Claim 42 is alleged to be incomplete. By virtue of its dependency on claim 41, Applicants note that this claim is properly directed to a composition comprising (i) the expression cassette of claim 1 and (ii) a Gag polypeptide. Thus, the claim is not incomplete as written.

In view of the above amendments, the teachings of the specification and the level of ordinary skill in the present art, the applicants submit that the boundaries of the pending claims are capable of being understood by one of ordinary skill in the art. Therefore, withdrawal of the rejections of the claims under 35 U.S.C. §112, second paragraph, is respectfully requested.

III. CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

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Please direct all further communications regarding this application to:

Anne S. Dollard, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2719
Facsimile: (510) 655-3542.

Respectfully submitted,

Date: March 13/02 By: Dasternak

Dahna S. Pasternak
Registration No. 41,411

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: 510-923-2719
Facsimile: 510-655-3542

Version Showing Changes Made to Claims

1. (Amended) An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an HIV *Gag* polypeptide, wherein the polynucleotide sequence encoding said *Gag* polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented as either nucleotides 844-903 of Figure 1 (SEQ ID NO:1) or nucleotides 841-900 of Figure 2 (SEQ ID NO:2).

2. An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an HIV *Gag* polypeptide, wherein the polynucleotide sequence encoding said *Gag* polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented as Figure 1 (SEQ ID NO:3) or Figure 2 (SEQ ID NO:4).

9. (Amended) The expression cassette of any of claim 2, wherein said polynucleotide sequence further includes a polynucleotide sequence encoding an HIV *polymerase* polypeptide, wherein the sequence encoding the HIV *polymerase* polypeptide is modified by deletions of coding regions [corresponding to] encoding reverse transcriptase and integrase.

10. (Amended) The expression cassette of claim 9, wherein said polynucleotide sequence [preserves] encodes a polypeptide comprising T-helper cell and CTL epitopes.

24. (Amended) A recombinant expression system for use in a selected host cell, comprising, [an] the expression cassette of claim 1, and wherein said polynucleotide sequence is operably linked to control elements compatible with expression in the selected host cell.

27. (Amended) A cell comprising [an] the expression cassette of claim 1, and wherein said polynucleotide sequence is operably linked to control elements compatible with expression in the selected cell.

41. (Amended) A composition for generating an immunological response, comprising:

[an] the expression cassette of claim 1.

49. (Amended) A method of immunization of a subject, comprising,

introducing [a] the composition of claim 41 into said subject under conditions that are compatible with expression of said expression cassette in said subject.

62. (Amended) A method of generating an immune response in a subject, comprising

introducing into cells of said subject [an] the expression cassette of claim 1, under conditions that permit the expression of said polynucleotide and production of said polypeptide, thereby eliciting an immunological response to said polypeptide.

63. (Amended) The method of claim 62, where the method further comprises administration of [an HIV-derived polypeptide] a polypeptide derived from an HIV.

67. (New) An expression cassette comprising a polynucleotide sequence of SEQ ID NO:1 or SEQ ID NO:2.

68. (New) An expression cassette comprising a polynucleotide sequence of SEQ ID NO:3.

69. (New) An expression cassette comprising a polynucleotide sequence of SEQ ID NO:4.

70. (New) The expression cassette of claim 68, further comprising a nucleotide sequence encoding an HIV protease polypeptide.

71. (New) The expression cassette of claim 69, further comprising a nucleotide sequence encoding an HIV protease polypeptide.

72. (New) The expression cassette of claim 68, further comprising a nucleotide sequence encoding an HIV polymerase polypeptide.

73. (New) The expression cassette of claim 69, further comprising a nucleotide sequence encoding an HIV polymerase polypeptide.

74. (New) A composition for generating an immunological response in a mammal comprising the expression cassette of claim 67.

75. (New) A method of generating an immune response in a mammal, the method comprising the step of intramuscularly administering the expression cassette of claim 67 to said mammal.